UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,562	07/06/2001	Katie Mary Binley	9192.16USWO	3021

23552 7590 11/26/2003

MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,562	BINLEY ET AL.	
	Examin r	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on th cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17-27 and 31* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-10,12-15,17-27 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Applicati n Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-4, 8-10, 12-15, 17-20 and 31, and elect species SEQ ID Nos. 9, 10 and HIF1-alpha in response filed 9-22-03 is acknowledged. The traversal is on the ground(s) that search for all the species would not impose serious burden on the examiner, for example, SEQ ID No. 10 is identical to nucleotides 7-18 of SEQ ID No. 11 and SEQ ID No. 2 is identical to nucleotide 4-22 of SEQ ID No. 1, and the special technical feature of HRE repeats with a spacer of at least 20 nucleotides is not in the prior art. This is not found persuasive because each SEQ ID No has different number of nucleotides and has different chemical structure, therefore, each SEQ ID No requires separate search. Hypoxia response enhancer element (HREE) derived from erythropoietin (EPO) was known in the art and said HREE contains 4 tandem repeats of HRE sequence and there are at least 20 nucleotides between the HIF consensus binding sites (e.g. US Pat. No. 5,834,306, column 6, SEQ ID No. 6).

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 5-7 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 9-22-03.

Applicants amended claims 21-27 to read on a vector comprising the polynucleotide of claim 1. Claims 21-27 will be joined to group I for examination, however, claims 23 and 24 are directed to distinct inventions having (i) nucleotide sequence encoding an inhibitory RNA molecule, (ii) one or more inhibitory RNA molecules, and (iii) a nucleotide sequence encoding a polypeptide capable of inhibiting the binding of VHL to Elongin B, Elongin C, or both. Only

"(iii)" will be examined in the present invention. Therefore, claims 23 and 24 will be examined only partially.

Applicants' preliminary amendment filed 3-19-01 and amendment filed 9-22-03 have been entered. Claims 2-15, 17-27 and 31 have been amended. Claims 16 and 28-30 have been canceled. Claims 1-15, 17-27 and 31 are pending and claims 1-4, 8-10, 12-15, 17-27 and 31 are under consideration. Claims 23 and 24 will be examined only partially.

Specification

3. The disclosure is objected to because of the following informalities: The nucleotide or amino acid sequences on page 11, 68-70, 76, 81, 82, 90, 98, 99, 108 and 109 and on Figure 14 are missing sequence identifier. A sequence identifier is needed for each sequence.

Appropriate correction is required.

Claim Objections

4. Claims 23 and 24 are objected to because of the following informalities: The term "VHL" is an abbreviation and can stand for numerous meanings. It is remedial to spell out the term "VHL". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "adapted to deliver the NOI" on lines 1 and 2 in claim 20 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "adapted to". It is unclear what kind of modification is required for the polynucleotide to be adapted to deliver the NOI. The specification fails to specifically define the phrase "adapted to".

7. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to introduce the polynucleotide into the genome of a virus, whether cells are required for the production of a virus, and whether the virus is produced or recovered during the process.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-4, 8-10, 12-15, 17-27 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-4, 8-10, 12-15, 17-27 and 31 are directed to a polynucleotide comprising at least two repeats, such as direct repeats, of a hypoxia response element (HRE), wherein the hypoxia-inducible factor (HIF) consensus binding sites within the two repeats are separated by a spacer of at least 20 nucleotides, a vector comprising the polynucleotide, and a method of producing a viral strain comprising introducing the polynucleotide into the genome of a virus. Claims 2 and 4 specify the HRE repeats are operably linked to a viral promoter, such as SV40 promoter. Claim 3 specifies the spacer sequence of SEQ ID No. 10 or 11. Claims 9 and 10 specify the HRE sequence of SEQ ID No. 1 or 2, or nucleotide sequence of SEQ ID No. 9. Claims 12, 15 and 17-19 specify the polynucleotide is operably linked to a nucleic acid of interest (NOI) encoding a cytotoxic polypeptide, a prodrug activating enzyme, a transcription factor, a metabolic enzyme, or a proliferation-regulating protein etc. Claim 14 specifies the promoter lacks a CAAT box sequence. Claims 23 and 24 specify the nucleotide sequence encodes a polypeptide capable of inhibiting the binding of VHL to Elongin B, Elongin C, or both. Claims 22 and 25-27 specify the vector is a viral vector, such as a retroviral vector, an adenoviral vector, or a lentiviral vector.

The specification indicates the use of the polynucleotide comprising the HRE and a therapeutic gene as a delivering vehicle for gene therapy in vivo and "a(A) preferred aspect of the present invention relates to uses of any of the aforementioned products in the treatment or prevention of a condition characterized by ischaemia, hypoxia or low glucose; particularly, but not exclusively, a condition such as cancer (in particular solid tumors), cerebral malaria, ischaemia heart disease or rheumatoid arthritis (e.g. specification, p. 1-9). The claimed polynucleotides and vectors must have a use and the only use indicated in the present invention

is gene delivery for gene therapy in vivo. Therefore, the claims read on gene therapy in vivo in light of the specification.

The specification fails to provide adequate guidance and evidence for how to use the claimed polynucleotides or vectors to deliver a therapeutic gene to a subject so as to provide therapeutic effect for gene therapy of various diseases via various administration routes in vivo. The specification also fails to provide the correlation between the therapeutic gene delivered in vivo, such as a nucleotide sequence encoding a HIF-1 (claim 13), a cytotoxic polypeptide (claims 17 and 18), a transcription factor, a metabolic enzyme, a proliferation-regulating protein or a heat shock protein (claim 19), a polypeptide capable of inhibiting the binding of VHL to Elongin B, Elongin C, or both (claim 23), or a nucleotide sequence encoding a non-functional derivative of wild type VHL (claim 24), and a particular disease or disorder.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reports that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus, far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (see page 239, right column). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3) and random integration of retroviral vector DNA into the host chromosome can lead to activation of unwanted genes or inactivation of transgenes (page 240, right column).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself

(volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use the claimed polynucleotides or vectors for gene therapy of various diseases so as to provide therapeutic effect in vivo via various administration routes.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (c) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claims 1, 2, 4, 8, 12, 15 and 17-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Ratcliffe et al., 1995 (WO 95/21927, IDS).

Claims 1, 2, 4, 8, 12, 15 and 17-21 are directed to a polynucleotide comprising at least two repeats, such as direct repeats, of a hypoxia response element (HRE), wherein the hypoxia-inducible factor (HIF) consensus binding sites within the two repeats are separated by a spacer of at least 20 nucleotides, and a vector comprising the polynucleotide. Claims 2 and 4 specify the HRE repeats are operably linked to a viral promoter, such as SV40 promoter. Claims 12, 15 and 17-19 specify the polynucleotide is operably linked to a nucleic acid of interest (NOI) encoding a

cytotoxic polypeptide, a prodrug activating enzyme, a transcription factor, a metabolic enzyme, or a proliferation-regulating protein etc.

Ratcliffe teaches a nucleic acid construct comprising at least a gene encoding a gene product having therapeutic activity to cells affected by disease, such as tumor cells, and at least one HRE or two or more HRE (P18 or P24), wherein the gene product can be a cytokine, a thymidine phosphorylase enzyme (prodrug activating enzyme), or growth factor (e.g. bridging p. 2-3, p. 4, 5, 7, 22). Ratcliffe teaches using three or more copies of one of the EPO or PGK sequences, or using longer portion of the EPO or PGK-1 enhancer or flanking sequence in the construct (e.g. p. 5). Ratcliffe also teaches using SV40 early promoter operably linked to EPO enhancer sequence in a plasmid (e.g. example I). When three P24 HRE sequence are used in a construct, the P24 in between two other P24 is considered a spacer and it is at least 20 nucleotides. Thus, claims 1, 2, 4, 8, 12, 15 and 17-21 are anticipated by Ratcliffe.

It should be noted that the intended use of the claimed polynucleotides or vectors as mentioned above under 35 U.S.C. 112 first paragraph rejection does not carry weight in 35 U.S.C. 102 rejection.

12. Claims 1, 2, 4, 8, 12, 15, 17-22, 25-27 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Webster et al., (US Patent No. 5,834,306).

Claims 1, 2, 4, 8, 12, 15, 17-22, 25-27 and 31 are directed to a polynucleotide comprising at least two repeats, such as direct repeats, of a hypoxia response element (HRE), wherein the hypoxia-inducible factor (HIF) consensus binding sites within the two repeats are separated by a spacer of at least 20 nucleotides, a vector comprising the polynucleotide, and a method of

producing a viral strain comprising introducing the polynucleotide into the genome of a virus. Claims 2 and 4 specify the HRE repeats are operably linked to a viral promoter, such as SV40 promoter. Claims 12, 15 and 17-19 specify the polynucleotide is operably linked to a nucleic acid of interest (NOI) encoding a cytotoxic polypeptide, a prodrug activating enzyme, a transcription factor, a metabolic enzyme, or a proliferation-regulating protein etc. Claims 22 and 25-27 specify the vector is a viral vector, such as a retroviral vector, an adenoviral vector, or a lentiviral vector.

Webster teaches a chimeric DNA construct comprising a hypoxia response enhancer element (HRE), such as erythropoietin HRE element (HREE1), a tissue specific promoter, and both of which are operably linked to a reporter gene or a therapeutic gene encoding bcl-2, NOS, catalase, SOD, or HSV thymidine kinase (e.g. abstract, column 117, 118). Webster also teaches an expression vector comprising a therapeutic gene encoding Bcl-2, SOD, or HSV thymidine kinase under the control of a ubiquitous promoter, such as SV40 promoter, or a tissue specific promoter, and further comprises HRE sequences, wherein the expression vector is a plasmid, an adenoviral vector, a retrovirus vector, adeno-associated vector, or herpes virus vector, and method of producing viral vectors (e.g. column 15-17). The nucleotide sequence of HREE1, SEQ ID No. 6, contains 4 tandem copies of HRE sequence and cloning linkers. The HRE sequence in between two HRE sequence is considered a spacer and there are at least 20 nucleotides between the HIF consensus binding sites within the two repeats of HRE sequences. Thus, claims 1, 2, 4, 8, 12, 15, 17-22, 25-27 and 31 are anticipated by Webster.

13. Claims 1, 2, 4, 8, 12, 13, 15, 17-22, 25-27 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Lewis et al., 1998 (WO 98/15294, IDS).

Claims 1, 2, 4, 8, 12, 13, 15, 17-22, 25-27 and 31 are directed to a polynucleotide comprising at least two repeats, such as direct repeats, of a hypoxia response element (HRE), wherein the hypoxia-inducible factor (HIF) consensus binding sites within the two repeats are separated by a spacer of at least 20 nucleotides, a vector comprising the polynucleotide, and a method of producing a viral strain comprising introducing the polynucleotide into the genome of a virus. Claims 2 and 4 specify the HRE repeats are operably linked to a viral promoter, such as SV40 promoter. Claims 12, 15 and 17-19 specify the polynucleotide is operably linked to a nucleic acid of interest (NOI) encoding a HIF-1, a cytotoxic polypeptide, a prodrug activating enzyme, a transcription factor, a metabolic enzyme, or a proliferation-regulating protein etc. Claims 22 and 25-27 specify the vector is a viral vector, such as a retroviral vector, an adenoviral vector, or a lentiviral vector.

Lewis teaches preparation of a hypoxia regulatable agent, such as a non-viral vector or a viral vector including an adenovirus vector, an adeno-associated viral vector, a herpes-virus vector or a retroviral vector, comprising a therapeutic gene encoding protein, such as a prodrug activation enzyme, a cytokine, or activator of angiogenesis, under the control of a HRE or a SV 40 promoter or both (e.g. p. 8, 14, 15, Figure 6). Lewis teaches that hypoxia regulated enhancer, e.g. a binding element for the transcription factor HIF-1, can be present in multiple copies and a gene encoding HIF-1-alpha may be included in the vector (e.g. p. 15). Lewis teaches HRE sequence from human Enolase A gene contains three HIF-1 consensus binding sites (e.g. p. 25, bottom). The HIF-1 binding sites C and D are separated by 28 bases (see Semenza et al., 1996,

J. Biol. Chem., 271: 32529-32537, Figure 6), therefore, there are at least 20 nucleotide spacer between the HIF consensus binding site within two HRE repeats. Thus, claims 1, 2, 4, 8, 12, 13, 15, 17-22, 25-27 and 31 are anticipated by Lewis.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.